UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,725	07/15/2003	Gregory M. Lanza	532512000401	1157

25225 7590 03/17/2008

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
BARHAM, BETHANY P	
ART UNIT	**PAPER NUMBER**
1615	

MAIL DATE	DELIVERY MODE
03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,725	LANZA ET AL.	
	Examiner	Art Unit	
	Bethany Barham	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71,75-79,82,85,86 and 94-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71,75-79,82,85,86 and 94-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt is acknowledged of the Applicant's Amended Claims, and Response filed on 12/11/2007. Claims 71, 75-79, 82, 85-86 and 94-97 are pending. Claims 71, 75-79, 82, 85-86 and 94-97 are rejected.

MAINTAINED REJECTIONS

The following are maintained rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71, 75-79, 82, 85-86 and 94-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There is no evidence in the instant specification that any and all of the proposed drugs are capable of being “contained in said layer and not carried or deposited in the core of said nanoparticle” and an explanation as to why a lipophilic drug will partition into the lipid layer and not into the liquid fluorocarbon core is

not shown. Based on the instant disclosure, it is the examiner's position that Applicants do not describe this invention in such a manner that would enable one of ordinary skill in the art to practice this invention without undue burden.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The instant claim 71 is directed to a method to deliver a drug to target tissue or organ comprising "nanoparticles comprising a core consisting of liquid fluorocarbon coated with a lipid/surfactant layer wherein said drug is contained in said layer and not carried or deposited in the core of said nanoparticle". Of which several compounds are listed as possible drugs anti-inflammatory, antirheumatic, neuromuscular blocker, sedative, antiallergic, hormone, antihelmintic, antimalarial, antituberculosis, immune serum, antitoxin, antivenom, rabies prophylaxis, bacterial vaccine, viral vaccine, etc (claims 87-92). It is the examiner's position that this claim is not supported by the instant specification.

The nature of the invention: The instant invention is directed to a method to deliver a drug to target tissue or organ comprising "nanoparticles comprising a core consisting of liquid fluorocarbon coated with a lipid/surfactant layer wherein said drug is contained in said layer and not carried or deposited in the core of said nanoparticle".

The state of the prior art: As set forth in 5,690,907 ('907), specific components such as phosphatipdylethanolamine and cholesterol can be incorporated into the lipid layer of a perfluorocarbon emulsion nanoparticle. Further, information from Kereos (http://www.kereos.com/technology.html) teaches that drug containing "hydrophilic payloads" are projected above the ligand-targeted emulsion surface and not contained within the layer and further that the lipophilic surface must be derivatives. Kereos also teaches that lipophilic payloads, such as many chemotherapeutics, are incorporated into the lipid monolayer. Not every drug is capable of being "contained in the lipid layer and not carried or deposited in the core", in fact not any and all lipophilic drugs are capable either. These particular compatible reaction partners are determined on the basis of experimentation. With a broad general disclosure, Applicants have not described how their invention would specifically work, specifically why a lipophilic drug would partition only into the lipid layer and not into the liquid perfluorocarbon core. Given the instant disclosure, one of ordinary skill in the art would have to resort to trial and error experimentation in order to practice the invention commensurate in scope with the claims.

The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current invention is capable of working with any and all drug compounds (hydrophilic and/or lipophilic). Guidance for preparing a nanoparticle comprising a specific hydrophilic drug doxorubicin and a specific lipophilic drug paclitaxel is provided in the specification (Examples 1-2 and 4). But as shown by Kereos a hydrophilic drug would be carried above the lipid layer and not incorporated into the lipid layer and the lipophilic layer must be derivatized. As a result, one of ordinary skill in the art would have to revert to trial and error experimentation in order to practice the invention commensurate in scope with the instant claim set. With respect to the instant composition, there is a substantial gap between a composition comprising a specific active agents and one comprising any and all active agents. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

The presence or absence of working examples: Guidance for preparing a nanoparticle comprising a specific hydrophilic drug doxorubicin and a specific lipophilic drug paclitaxel is provided in the specification (Examples 1-2 and 4).

The quantity of experimentation: In the instant case, there is a substantial gap between a nanoparticle comprising a specific drug such as doxorubicin and one comprising any and all drug compounds (hydrophilic and/or lipophilic). Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to

bridge this gap. In order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. The instant disclosure is broad and generic. It is not clear what specific embodiments would be required in order for one of ordinary skill in the art at the time the invention was made to practice the instant invention commensurate in scope with the claims.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Response to Arguments

Applicant's arguments filed on 12/11/2007 have been fully considered but they are not persuasive. Applicant claims the 'drug is confined to said layer and not carried or deposited in the core of said nanoparticle', but all the instant claimed drugs are not all hydrophobic so how can one of skill in the art 'control' where they go? Applicant has not provided evidence for why there is no lipophilic drug incorporated into the perfluorocarbon core which is hydrophobic. Doxorubin is water soluble and so it partitions but what about the drug paclitaxel which is hydrophobic, will it not also go into the hydrophobic core? The Office is not equipped for experiments and as such the burden falls to Applicant to submit factual evidence showing that a lipophilic drug would not also be present in the hydrophobic core, as the MPEP 2112 states: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is

based on 'inherency' under 35 U.S.C. 102, on '*prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). While MPEP 2113 states: "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 71, 75-79, 82, 85-86 and 94-97 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,690,907, US 5,780,010, or US 5,958,371 as evidenced by US 4,595,680, US 5,656,287, or US 6,149,937.

- Lanza in these patents discloses a method of delivery of an active agent to the target site using the same emulsions. The emulsions are oil-in-water emulsions containing a ligand (avidin, antibodies), an active agent, and perfluorococtytbromide. The particles are coated with a lipid/surfactant. The lipids include phospholipids such as phosphatidylcholine, fatty acids (anionic) and stearylamine (cationic). It should be noted that applicant views phosphatidylcholine (1,2 diacyl-snoglycerol-3-ethylphosphocholine) as a cationic lipid (see original canceled claim 15).
- The particles are of instant sizes (note the abstract, col. 4, line10 through col. 6, line 46, Col. 7, line 48 et seq,, Examples and claims of 907; col. 4, line 25 through col. 8, line 9, Examples and claims of 010 and 371).
- As set forth in '907, biotinylated phosphatidylethanolamine and cholesterol are incorporated into the outer lipid monolayer of the perfluorocarbon emulsion nanoparticles (Example 2; column 8, lines 66-67). As evidenced by '680, phosphatidylethanolamine can be considered to be a drug, having activity against disorders related to the central nervous system ('680 abstract). Thus, '907 explicitly teaches the incorporation of a drug, phosphatidylethanolamine

and/or cholesterol, into the outer lipid layer of a perfluorocarbon emulsion nanoparticle. Additionally, '907 also disclose combining the ligand-based perfluorocarbon emulsion nanoparticle system with chemotherapeutic agents or other drugs (column 7, lines 48-67).

- A specific example of the drugs set forth by '907 is doxorubicin (column 7, line 54). Doxorubicin is a lipophilic drug that would have a tendency to incorporate into a lipid layer of a nanoparticle (See US 5,656,287 - column 2, lines 31-54 and US 6,149,937 - column 1, lines 53-67). Because the instant ligand-based perfluorocarbon emulsion nanoparticle system can be considered to be a liposome (See US 5,656,287; column 4, line 27), the use of US 5,656,287 and US 6,149,937 to show where the lipophilic drug would have the propensity to migrate is proper. Like the instant method of claim 1, the lipid-encapsulated particles (also referred to as liposome at column 4, line 27) are attached to a ligand-targeting moiety and may be used to target tissue surfaces (abstract and column 2, lines 54 - 56). Consistent with the instant specification, since microparticles comprising targeting ligand moieties would have the ability to bind to a cellular surface (including tissue) and remain stationary or "affixed," thereby interacting with the cell surface over an extended period of time, the examiner respectfully asserts that delivery of a drug or biological species would be inherently facilitated (page 7, lines 21-27 of the instant specification).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 71, 75-79, 82, 85-86 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over by US 5,690,907 ('907) in view of US 4,595,680 ('680), US 5,656,287 ('287), or US 6,149,937 ('937).

The limitations of claims 71, 75-79, 82, and 85-86 are taught:

- The teachings of Lanza '907, have been discussed above. What is lacking in Lanza is the explicit teaching that the active agents are incorporated in the lipid layer. However, since a lipophilic active agents such as taxanes, paclitaxel and doxorubicin have a tendency to dissolve in lipid material and not in an aqueous medium, it would have been obvious to one of ordinary skill in the art that the active agents taught by Lanza would be in the lipid layer.
- A specific example of the drugs set forth by '907 is doxorubicin (column 7, line 54). Like the instant method of claim 1, the lipid-encapsulated particles (also referred to as liposome at column 4, line 27) are attached to a ligand-targeting moiety and may be used to target tissue surfaces (abstract and column 2, lines 54 - 56). Consistent with the instant specification, since microparticles comprising targeting ligand moieties would have the ability to bind to a cellular surface

(including tissue) and remain stationary or "affixed," thereby interacting with the cell surface over an extended period of time, the examiner respectfully asserts that delivery of a drug or biological species would be facilitated (page 7, lines 21-27 of the instant specification).

- Further, '907 teaches the well known method of adding components to a solvent such as chloroform, evaporating the solvent off to form a film and then sonicating the mixture resulting in a liposome suspension (Examples).
- '907 does not teach that PE is a drug or that doxorubicin would incorporate into the lipophilic layer. '907 does not teach the drugs claims in instant claims 87-93.
- '680 teaches that phosphatidylethanolamine can be considered to be a drug, having activity against disorders related to the central nervous system (abstract), as shown above a drug is defined as a substance used as a medication or in the preparation of medication (Merriam-Webster Dictionary).

The limitations of claims 94-97 are taught:

- '287 and '937 teach that doxorubicin is a lipophilic drug that would have a tendency to incorporate into a lipid layer of a nanoparticle (See '287 - column 2, lines 31-54 and '937 - column 1, lines 53-67). Because the instant ligand-based perfluorocarbon emulsion nanoparticle system can be considered to be a liposome (See '287; column 4, line 27), the use of '287 and '937 to show where the lipophilic drug would have the propensity to migrate is proper. '287 while disclosing the liposomal preparation of cyclosporin teaches that water-soluble molecules get incorporated into the aqueous interiorand the lipophilic molecules

will tend to be incorporated into the lipid layer. The process of preparation is similar to instant process (see instant example 1), that is, dissolving the phospholipid and the lipophilic active agent in chloroform, drying the lipid mixture and the addition of the aqueous layer (col. 2, lines 31-54).

- '937 also teaches that amphiphilic drugs such as actinomycin D, vinblastine, bupivacine are associated in the lipid layers, leading to increased efficacy (col. 2, lines 42). Other drugs in '937 taught to have similar amphiphilic character are anaesthetics (such as prilocaine, etidocaine), narcotic analgesics (such as morphine, fentanyl), and more generally amphiphilics endowed with one pK between pH 3.5 and 10.5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of '907, with '680, '287 or '937. All teach incorporating drugs into a liposome type system. One of ordinary skill in the art would have been motivated to combine '907, which teaches the ligand-based perfluorocarbon emulsion nanoparticle system comprising phosphatidylethanolamine and cholesterol, and are taught to be drugs in '680, with chemotherapeutic agents or other drugs, such as doxorubicin ('907 column 7, lines 48-67). '287 and '937 teach doxorubicin would have a tendency to incorporate into a lipid layer of a nanoparticle. As such, it would have been obvious to incorporate other drugs taught by '287 and '937 with a reasonable expectation of success of incorporating the drug into the lipid layer of the nanoparticle of '907. It would have been obvious to one of ordinary skill in the art that the lipophilic active agents in Lanza are trapped in the lipid layer since similar method involving

organic solvent and the addition of an aqueous medium to the lipid mixture containing the lipophilic active agent results in the incorporation of the agent in the lipid layer as evident from '680, '287, or '937.

Response to Arguments

Applicant's arguments filed on 12/11/2007 have been fully considered but they are not persuasive. In response to the 06/27/2006, 10/31/2006 and 8/20/2007, Applicant's assert that US 5,690,907, US 5,780,010, and US 5,958,371 do not anticipate or are not obvious over the instant claim set. In making this assertion, the Applicants assert that the drugs set forth in US 5,690,907 are not inherently present in the lipid portion of the nanoparticles and that it is not a drug. The examiner respectfully disagrees with this assertion. As noted in the above rejection, biotinylated phosphatidylethanolamine is incorporated into the outer lipid monolayer of the perfluorocarbon emulsion nanoparticles disclosed in US 5,690,907 (Example 2; column 8, lines 66-67). As evidenced by US 4,595,680, phosphatidylethanolamine can be considered to be a drug, having activity against disorders related to the central nervous system (abstract). Merriam-Webster Dictionary defines drug to be "(i) a substance used as a medication or in the preparation of medication; (ii) according to the Food, Drug, and Cosmetic Act (1) : a substance recognized in an official pharmacopoeia or formulary (2) : a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (3) : a substance other than food intended to affect the

structure or function of the body (4) : a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device." (http://www.m-w.com/cgi-bin/dictionary?drug)

Thus, US 5,690,907 explicitly teaches the incorporation of a drug, phosphatidylethanolamine (a substance used as a medication or in the preparation of medication), into the outer lipid layer of a perfluorocarbon emulsion nanoparticle. Additionally, US 5,690,907 also disclose the steps instant claimed in amended claim 71 (example 1) and combining the ligand-based perfluorocarbon emulsion nanoparticle system with chemotherapeutic agents or other drugs (column 7, lines 48-67). A specific example of the drugs set forth by US 5,690,907 is doxorubicin (column 7, line 54). Doxorubicin is a lipophilic drug that would have a tendency to incorporate into a lipid layer of a nanoparticle (See US 5,656,287 - column 2, lines 31-54 and US 6,149,937 - column 1, lines 53-67). '287 while disclosing the liposomal preparation of cyclosporin teaches that water-soluble molecules get incorporated into the aqueous interior and the lipophilic molecules will tend to be incorporated into the lipid layer. The process of preparation is similar to instant process (see instant example 1), that is, dissolving the phospholipid and the lipophilic active agent in chloroform, drying the lipid mixture and the addition of the aqueous layer (col. 2, lines 31-54). However, since a lipophilic active agents such as taxanes and doxorubicin have a tendency to dissolve in lipid material and not in an aqueous medium, it would have been obvious to one of ordinary skill in the art that the active agents taught by Lanza would be in the lipid layer.

Because the instant ligand-based perfluorocarbon emulsion nanoparticle system can be considered to be a liposome (See US 5,656,287; column 4, line 27), the use of US 5,656,287 and US 6,149,937 to show where the lipophilic drug would have the propensity to migrate is proper. As such, the examiner respectfully asserts that the above rejection is proper. It should be noted that, because there is no claim language indicating that the instant nanoparticles are hydrophobic (as discussed in the 1/26/2006 Remarks section), the nanoparticle of claim 1 is being viewed as a liposome-type formulation (also consistent with the description of the nanoparticle as a liposome in See US 5,656,287; column 4, line 27).

Conclusions

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bethany Barham whose telephone number is (571)272-61755. The examiner can normally be reached on M-F, 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bethany Barham
Art Unit 1615

/Michael P Woodward/
Supervisory Patent Examiner, Art Unit 1615